EXPEDITED PROCEDURE REQUESTED
EXAMINING GROUP 1644
PATENT
Customer No. 22,852
Attorney Docket No. 06478.1507-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	DO NOT ENTER: /Y.K./
Reinhard BOLLI *et al.*	) Group Art Unit: 1644	
	)	
Application No.: 10/579,357	) Examiner: Yunsoo Kim	08/05/2009
	)	
Filed: May 16, 2006	)	
	) Confirmation No.: 2138	
For: IMMUNOGLOBULIN	)	
PREPARATIONS HAVING	)	
INCREASED STABILITY	)	**VIA EFS WEB**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.116

In reply to the Final Office Action dated May 5, 2009, Applicants respectfully request reconsideration of this application in view of the following amendments and remarks.

Amendments to the claims begin on page 2 of this paper

Remarks/Arguments follow the amendment section of this paper and begin on page 7.

Attachments include an **Amendment Transmittal** and extra claims fees.

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A stable ~~immunoglubulin~~immunoglobulin preparation, wherein the preparation comprises immunoglobulin, a stabilizer comprising proline, ~~and~~ wherein the preparation has a pH of about 4.2 to about 5.4, and wherein the preparation does not comprise nicotinamide.

2-3. (Cancelled)

4. (Previously presented) The preparation of claim 1, wherein proline is L-proline.

5. (Currently amended) The preparation of claim 1, wherein said preparation has a pH of about 4.5 to about 5.2.

6. (Currently amended) The preparation of claim 5, wherein said preparation has a pH of about 4.6 to about 5.0.

7. (Currently amended) The preparation of claim 1, wherein the ~~final~~ concentration of proline in the preparation is at least 0.2 M.

8. (Currently amended) A stable immunoglobulin preparation, wherein said preparation comprises immunoglobulin, a stabilizer comprising proline, ~~and~~ wherein the preparation has a pH of about 4.2 to about 5.4, and wherein the ~~final~~ concentration of proline in the preparation is ~~between~~ from 0.2 to 0.4 M.

9. (Currently amended) The preparation of claim 1 or 8, wherein the ~~final~~ concentration of proline is 0.25 M.

10. (Previously presented) The preparation of claim 1 or 8, wherein the immunoglobulin concentration of said preparation is from 5 to 25% w/v.

11. (Currently amended) The preparation of claim 10, wherein the immunoglobulin concentration of said preparation is from 15 to 20% w/v ~~for subcutaneous administration~~.

12. (Currently amended) The preparation of claim 10, wherein the immunoglobulin concentration of said preparation is from 6 to 15% w/v~~, for intravenous administration~~.

13. (Previously presented) The preparation of claim 12, wherein the immunoglobulin concentration of said preparation is from 8 to 12% w/v.

14. (Cancelled)

15. (Previously presented) The preparation of claim 1 or 8, wherein said preparation is an IgG, IgA or IgM preparation.

16. (Previously presented) A pharmaceutical composition comprising the immunoglobulin preparation of claim 1 or 8 and pharmaceutically acceptable additives.

17. (Cancelled)

18. (Withdrawn - currently amended) A method of stabilising immunoglobulin preparations, comprising providing an aqueous immunoglobulin solution and adding

proline, wherein the pH of the solution is adjusted to a pH of about 4.2 to about 5.4, and wherein the preparation does not comprise nicotinamide.

19. (Cancelled)

20. (Withdrawn) The method of claim 18, wherein the pH is adjusted to 4.8.

21. (Withdrawn - Currently amended) The method of claim 18, wherein the final concentration of the proline in the preparation is ~~adjusted to between~~ from 0.2 to 0.4 M.

22. (Cancelled)

23. (Previously presented) A pharmaceutical composition comprising the immunoglobulin preparation of claim 1 and pharmaceutically acceptable additives.

24. (Withdrawn - currently amended) A method of decreasing aggregate formation and/or of decreasing colouring of immunoglobulin preparations, comprising providing an aqueous immunoglobulin solution and adding ~~one or more stabilisers chosen from non-polar amino acid~~ proline, wherein the pH of the solution is adjusted to a pH of about 4.2 to about 5.4.

25. (Withdrawn - Currently amended) The method of claim ~~25~~24, wherein the pH is adjusted to 4.8.

26. (Cancelled)

27. (Withdrawn - Currently amended) The method of ~~claim 26~~ claim 24, wherein the proline concentration is adjusted to ~~between~~ from 0.2 to 0.4 M.

28. (Currently Amended) The preparation of claim 1 or 8, wherein the ~~final~~ concentration of proline in the preparation is ~~between~~ from 0.2 to 0.3 M.

29. (New) The preparation of claim 15, wherein the preparation is an IgG preparation.

30. (New) The preparation of claim 29, wherein the concentration of IgG in the preparation is 8-12% w/v.

31. (New) The preparation of claim 30, wherein the concentration of IgG in the preparation is 10% w/v.

32. (New) The preparation of claim 29, wherein said preparation has a pH of about 4.6 to about 5.0.

33. (New) The preparation of claim 29, wherein said proline is L-proline, and the concentration of L-proline in the preparation is from 0.2 to 0.3 M.

34. (New) The preparation of claim 29, wherein the preparation is a liquid preparation and has not been subject to lyophilization.

35. (New) The preparation of claim 1 or 8, wherein the preparation is an IgG preparation, the proline is L-proline and the concentration of the L-proline in the preparation is from 0.2 to 0.4 M, and wherein the concentration of IgG in the preparation is 6-15% w/v.

36. (New) The preparation of claim 35, wherein the preparation is a liquid preparation that has not been subject to lyophilization.

37. (New) The preparation of claim 1 or 8, wherein the preparation is an IgG preparation, the preparation has a pH of about 4.6 to about 5.0, the proline is L-proline and the concentration of the L-proline in the preparation is from 0.2 to 0.3 M, and wherein the concentration of IgG in the preparation is 8-12% w/v.

38. (New) The preparation of claim 37, wherein the preparation is a liquid preparation that has not been subject to lyophilization.

39. (New) The immunoglobulin preparation of claim 1 or 8, wherein the preparation is an IgG preparation, the proline is L-proline and the concentration of the L-proline in the preparation is from 0.2 to 0.4 M, and wherein the concentration of IgG in the preparation is 15-20% w/v.

40. (New) The preparation of claim 39, wherein the preparation is a liquid preparation that has not been subject to lyophilization.

REMARKS

I. Status of the claims

Prior to the entry of this amendment, claims 1, 4-13, 15, 16, 18, 20, 21, and 23-25, and 27-28 were pending in the application. Claims 18, 20, 21, 24-25, and 27 have been withdrawn by the Examiner as directed to non-elected subject matters.

By this amendment, Applicants have amended claims 1 and 8 to make it clear that the proline referred to in the claims is separate from the immunoglobulin protein molecules. Exemplary support for the amendments can be found throughout the specification, for example, at page 4, lines 1-7. Applicants also amended claims 1, 5-9, 11, 12, 18, 21, 25, 27 and 28 to remove redundant phrases, correct minor typographical errors, or clarify the pH or the concentration ranges recited in the claims. Without prejudice and disclaimer, withdrawn claim 24 has been amended to recite the provision in claim 26. Claim 26 is thus cancelled without prejudice and disclaimer.

Applicants also add claims 29-40, which are fully supported and enabled by the originally filed specification. For instance, exemplary support can be found:

- at page 5, line 16 for the recited IgG;
- at page 6, lines 18-23 for the recited concentration of IgG;
- at page 5, lines 26-32 for the recited pH ranges;
- at page 6, lines 5-8 for the recited proline concentration; and
- at page 5, lines 9-12 for the recitation of "a liquid preparation that has not been subject to lyophilization."

Accordingly, no new matter has been introduced.

Applicants submit that the amendments do not raise new issues or require an additional search of the art. Therefore, this Amendment should allow for immediate action. Applicants further submit that the entry of the amendment would place the application in better form for appeal, should the Office dispute the patentability of the pending claims. Thus, Applicants request entry of the amendments according to 37 C.F.R. § 1,116.

Applicants also thank the Office for withdrawing the rejections made in the Office Action mailed September 26, 2008. Office Action at page 2.

II. Rejections under 35 U.S.C. § 102

A. The '586 patent

The Office rejects claims 1, 4-6, 15, 16, and 23 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,171,586 to Lam et al. ("the '586 patent") for the reasons as set forth at page 4 of the Office Action. Specifically, the Office alleges that "[i]t is noted that the claimed invention as currently amended does not recite a stable immunoglobulin preparation comprising an immunoglobulin and a proline as a stabilizer. The claimed immunoglobulin preparation reads on an antibody preparation with an amino acid residue proline in the amino acid sequence with pH 4.2-5.4 in the absence of nicotinamide." *Id.* Applicants respectfully disagree with and traverse the rejection.

Nevertheless, solely in an attempt to advance the prosecution, Applicants have amended claim 1 to make it clear that proline referred to in the claims is separate from the immunoglobulin molecule. The '586 patent does not teach an immunoglobulin preparation that comprises a stabilizer comprising proline, as recited in claim 1, as amended. Accordingly, the '586 patent does not teach each and every element of

independent claim 1 and claims 4-6, 15, 16, and 23 depend thereupon. Withdrawal of the § 102 rejection is respectfully requested.

B. The '139 publication

The Office rejects claims 1, 4-8, 10-13, 15, 16, and 23 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2005/0142139 to Schulke *et al.* ("the '139 publication") for the reasons as set forth at page 4 of the Office Action. Applicants respectfully disagree with and traverse the rejection for the following reasons.

In order to show anticipation, the Office must show that a single reference discloses, either expressly or inherently, each and every element of the pending claims. *See* M.P.E.P. § 2131. Applicants submit that the rejection over the '139 publication fails to meet this requirement.

The presently claimed invention is directed to an **immunoglobulin** preparation. The '139 publication, however, is directed to liquid and lyophilized formulations of a **CD4-IgG2 chimeric heterotetramer**. *See* the '139 publication, paragraph [0003]. As described in the '139 publication, CD4-IgG2 "is a novel chimeric protein in which polypeptides comprising both the heavy and light chains constant regions of human IgG2 have been fused to the V1 and V2 gp120-binding domains of human CD4." *Id.*, paragraph [0005]. Accordingly, CD4-IgG2 is a fusion protein and **not** an "immunoglobulin" as defined herein. (*See, e.g.*, page 5, lines 14-24, and Example 2, at pages 9-11.) Nor is that protein an "IgG" as recited in the newly added claims 29-39. For instance, those of ordinary skill know that IgG is a monomeric protein and that one of the concerns in formulating IgG's is the appearance of unwanted aggregates,

including dimers. In contrast, the protein described in the '139 publication is designed to be a chimeric tetramer.

Furthermore, independent claims 1 and 8 recite, *inter alia*, an immunoglobulin preparation that "has a pH of **about 4.2 to about 5.4**." The '139 publication, however, merely discloses pharmaceutical formulations with a pH of between about **5.5-6.5**. *See* the '139 publication, paragraph [0009] (emphasis added). Accordingly, the pH of the '139 publication's pharmaceutical formulation does not overlap with the pH of the presently claimed immunoglobulin preparations.

For at least the forgoing reasons, the '139 publication does not disclose each and every element of the present application. The rejection is improper and should be withdrawn.

III. Rejections under 35 U.S.C. § 103

The Examiner rejects claims 1, 7-9, and 28 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '139 publication. Office Action at page 5. Applicants respectfully disagree with and traverse the rejection for the following reasons.

As mentioned above, the '139 publication is directed to liquid and lyophilized formulations of a specific, novel fusion protein, **CD4-IgG2 chimeric heterotetramer**, and not of immunoglobulins. Those are different proteins with different structures and different chemical and physical properties, as discussed above. Accordingly, one cannot reasonably predict if a formulation used for the protein described in the '139 publication could be successfully used for a different protein with different structure and properties. For that reason, the '139 publication is not applicable to one of ordinary skill wishing to formulate an immunoglobulin preparation.

For that reason alone, this rejection should be withdrawn.

Indeed, following the Supreme Court's decision in *KSR v. Teleflex*, the Office has announced seven ways in which a set of prior art may be combined in an obviousness rejection. *See* 72 Fed. Reg. 57,526 (Oct 10, 2007). In each one, the Office must show that one of ordinary skill in the art would conclude - from the combination of the art alone, with no reference to the patent application at issue - that the outcome of the combination would be predictable or that there would be a reasonable expectation of success. The present rejection fails this predictability requirement.

But even if, merely for the sake of argument, the '139 publication were applicable to the present invention, the '139 publication teaches away from the instant claims in several respects. It teaches a different pH range than claimed here, its formulations require a histidine buffer not required here, it teaches that glycine and alanine are superior stabilizers compared to other amino acids such as proline used here, and it teaches a different concentration of amino acid stabilizer.

Specifically, the '139 publication teaches that its pharmaceutical formulation has a pH of between about 5.5-6.5 and **not** about 4.2 to about 5.4 as recited in independent claims 1 and 8. Further, the '139 inventors state that they had conducted an experiment to evaluate the effect of pH on the stability of their formulation. *See* the '139 publication, paragraphs [0073], [0074], and [0126]. In doing so, the '139 publication describes that "[t]o evaluate the effect of pH, samples in base buffer and approximately 25 mM NaCl at pH's ranging from 4 to 8 and a sample in PBS were incubated at 50° C. for 0, 3, or 7 days and analyzed." *Id.* paragraph [0126]. The '139 publication then reports that:

> All samples showed some degree of suspended precipitate at day 7. On days 3 and 7, samples at pH 7.5 and 8 were

> cloudy with precipitate. HPLC-SEC analysis showed that **samples in buffers at pH 6 and 6.5 yielded the highest recoveries (~80%) of CD4-IgG2 monomer at day 7 compared to ~25-55% recovery at other pH values.** The RALS data suggested that the optimal pH range for CD4-IgG2 was 5.5-7. Measurement of EF showed that pH 6 overall exhibited the highest emission ratios, indicating less hydrophobicity and less denaturation. Thus, **the optimal pH for maintaining protein stability was determined by apparent hydrophobicity analysis to be pH 6**. However, subjecting samples to shear stress and measuring CD4-IgG2 monomer recovery by HPLC-SEC, recovery of total protein by UV spectroscopy, and **turbidity by RALS, suggested that CD4-IgG2 could best withstand shear stress at pH 6.5**.

Id. (emphasis added). Thus, the '139 publication specifically teaches that the samples in buffers at pH 6 and 6.5 yielded the highest recoveries as compared to the other pH values. This is in contrast to the presently claimed pH range of about 4.2 to about 5.4.

Second, the '139 publication requires the presence of histidine buffer to maintain the stability of its **CD4-IgG2** formulation. The present claims, however, do not require such a buffer. *See id.,* paragraphs [0008]-[0013].

Third, while the '139 publication states that its formulation may further comprise an amino acid stabilizer that could be selected from alanine, glycine, proline, and glycylglycine, the '139 publication fails to provide any teaching or suggestion that would have prompted a skilled artisan to specifically choose proline as a stabilizer. To the contrary, the working examples of the '139 publication mostly contain glycine as an amino acid stabilizer. *See id.*, Tables 2-4 and 7-9. Indeed, in evaluating the effect of amino acid stabilizers, the '139 publication states that "[g]lycine and alanine showed slightly higher percentage recoveries than the other histidine-based formulation." *Id.*, paragraph [0138].

Fourth, as conceded by the Examiner, the '139 publication merely teaches that its amino acid stabilizing agent is present at a concentration of between about 25-150 mM. While "about 150 mM" may be close to 200 mM, a skilled artisan would have had no reason nor motivation to increase the concentration of the '139 publication's amino acid stabilizer beyond 0.2 mM, such as 0.2-0.4 mM as recited in claim 8, or 0.25 mM as recited in claim 9. As stated in the Declaration of Reinhard BOLLI filed February 9, 2009, "a skilled artisan would have no reason nor motivation to increase the proline concentration beyond 200 mM because it would increase the cost of the preparation and the osmolarity of the solution, both of which could have led to undesirable outcomes for clinical applications." *Id.*, ¶ 13. Likewise, if, only for the sake of argument, the '139 publication were applicable to the instant claims, a skilled artisan would have had no motivation whatsoever to move in the direction of the present claims.

For the forgoing reasons, the Office fails to establish a *prima facie* case of obviousness in view of the '139 publication. Accordingly, Applicants respectfully request the Office to withdraw this rejection.

IV. Conclusions

In view of the foregoing remarks, Applicants submit that the claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration of this application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: August 4, 2009

By: _____
Elizabeth A. Doherty
Reg. No. 50,894